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EXAMINER	
REDDIG, PETER J	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,224	MUELLER-HERMELINK ET AL.	
	Examiner	Art Unit	
	Peter J. Reddig	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/30/2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *111-130 and 133-154* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *111-130 and 133-154* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 30, 2008 has been entered. Claims 111-114, 116-118 have been amended and new claims 135-154 have been added. Claims 111-130 and 133-154 are currently being examined.

Declaration

2. The Declaration of Dr. Mueller-Hermelink and Dr. Vollmers under 37 CFR 1.132 filed September 30, 2008 is sufficient to overcome the rejection of claims based upon Brändlein et al. (Human Antibodies, 18 April 2003, 11:107-119), publication date shown in Appendix 1.

3. The Declaration of Dr. Mueller-Hermelink and Dr. Vollmers under 37 CFR 1.132 filed September 30, 2008 is insufficient to overcome the rejection of claims 111-122 and 126-132 based upon by Brändlein et al. (Amer. Assoc. Can. Res., March 29, 2002, 43:970, abstract #4803, IDS) as set forth in the last Office action because: The reference is a statutory bar.

Rejections Maintained

Priority

4. The priority date for claims 111-122 and 124-130 remains and for new claims 135-154 is July 2, 2003 and the priority date for claims 123, 133, and 134 remains July 6, 2002.

Applicants argue that they respectfully do not concede the issue of priority for the claims. In particular, for example, support for claims that refer to variant sequences, including modifications and substitutions can be found throughout DE 102 30 516.1, filed July 4, 2002. For example, claim 1 recites that the antibody comprising heavy and light chain molecules, in which "at least one variable region of the light chains has substantially the amino acid sequence stated in Appendix 2 and/or at least one variable region of the heavy chains has substantially the amino acid sequence stated in Appendix 1." Claim 8 is directed to antibodies and functional fragments according to claims 1 to 7 "characterized in that individual amino acid groups are substituted, and/or inserted, and/or removed." Furthermore, DE 102 30 516.1 discloses that "the present invention encompasses minor modifications or substitutions of the chains" at page 3, paragraph [0010] Moreover, DE 102 30 516.1 discloses that "the characteristics of the antibody or the functional fragments thereof may be modified by substituting and/or inserting and/or removing individual amino acid groups" at page 4, paragraph [0022] Thus, it is clear that the present scope of the claims are adequately supported by DE 102 30 516.1, filed July 4, 2002.

Applicants arguments have been considered, but have not been found persuasive because the cited support does not support the broadly claimed antibodies that bind to an epitope of the 55 kDA or 115kDA protein expressed by ASPC-1 cells or the BXPC-3 cells, wherein the PM2 antibody binds to said epitope of the polypeptide having an approximate molecular weight of 115 kDa expressed by ASPC-1 cells or the BXPC-3 cells and the specific variants claimed in the dependent claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 121 and 124 remain rejected and claims 145 and 148 is rejected under 35 U.S.C. 112, first paragraph the reasons previously set forth in section 5, pages 4-10 of the Office Action of March 31, 2008.

Examiner argued:

Applicants argue that the Examiner has acknowledged that the level of knowledge and skill with respect to antibody structure and function at the time of the invention was high. For example, as discussed at length in the Office Action the role of antibody heavy and light chain variable regions, particularly CDRs and FRs, in antigen binding were well understood by the skilled artisan at the time of the invention (see, for example, pages 9-11 of the Office Action). The specification also discloses the role of antibody heavy and light chain variable regions, CDR and FR regions in antigen binding (page 22, line 6, to page 23, line 2). Consequently, in view of the high level of knowledge and skill in the art with respect to antibody structure and function at the time of the invention clearly the skilled artisan would be apprised of antibody regions that participate in antigen binding.

Applicants' arguments have been considered, but have not been found persuasive. Although antibody structure is well known in the art, the cited references demonstrate that single amino acid changes can unpredictably disrupt the function of an antibody. Thus, given the unpredictability of making the broadly claimed antibody that is functional, one of skill in the art would not believe it more likely than not that the broadly claimed antibody would function as claimed.

Applicants argue that in addition to the high level of knowledge and skill in the art with respect to antibody structure and function, as acknowledged by the Examiner the specification discloses the locations of the CDRs in SEQ ID NOs: 5 and 7 (page 7 of the Office Action). In particular, the specification discloses the CDRs in SEQ ID NOs: 5 and 7 in Figures 14 and 15 (see, also, pages 5, lines 6-7 and 24-25). Furthermore, in view of the fact that the specification discloses the location of the CDRs in SEQ ID NOs: 5 and 7 and that SEQ ID NOs: 5 and 7 are human sequences, the skilled artisan would know the location of the FRs in SEQ ID NOs: 5 and 7. Applicants argue that in view of the above guidance, the skilled artisan would know the location of CDRs and FRs of SEQ ID NO: 5 and 7.

Applicants' arguments have been considered, but have not been found persuasive. Although the skilled artisan would know the location of CDRs and FRs OF SEQ ID NO: 5 and 7, one of skill in the art would not predictably be able to make all of the claimed variants for the reasons previously set forth previously and above given the unpredictability of sequence changes on the binding activity of the antibody.

Applicants argue that because the knowledge and skill in the art at the time of the invention was high in terms of antibody structure and function and the location of sequences in

SEQ ID NOs: 5 and 7 that contribute to antigen binding would be known, the skilled artisan would also know residues in SEQ ID NOs'5 and 7 that would be amenable to substitution and therefore, be able to predict with reasonable certainty variants of SEQ ID NOs: 5 and 7 that would have at least partial binding activity. As a non-limiting example illustrating this point, the skilled artisan would know that an amino acid substitution, such as a conservative substitution, for example, outside of a CDR or FR region of in SEQ ID NOs: 5 and 7 would likely not destroy antigen binding activity. Thus, the skilled artisan could make a conservative substitution of either SEQ ID NOs: 5 or 7 outside of a CDR or FR with a reasonable certainty that the substituted sequence would retain at least partial antigen binding activity. Given the large number of amino residues outside of CDR and FR regions, and the number of amino residues outside of antibody variable regions, clearly many variants of SEQ ID NOs:5 and 7 could be readily produced that have at least partial antigen binding activity. As an additional non-limiting example illustrating this point, the skilled artisan would know that given the role of CDRs in antibody binding a large number of non-conservative amino acid substitutions in the CDRs in SEQ ID NOs: 5 and 7 would likely reduce or eliminate antigen binding. Thus, the skilled artisan would know not to delete or introduce a large number of non-conservative substitutions into the CDRs in SEQ ID NOs: 5 and 7. Consequently, in view of the guidance in the specification and the high level of knowledge and skill in the art regarding antibody structure and function, the skilled artisan would know of general regions and particular residues that would be more or less amenable to substitution and could therefore predict SEQ ID NOs: 5 and 7 variants likely to have at least partial antigen binding activity without actually having to produce such variants and fragments.

Applicants' arguments have been considered, but have not been found persuasive because, contrary to Applicants' arguments, one of skill in the art would not predictably know where to make the broadly claimed changes given the unpredictability in the art previously set forth and the lack of guidance provided in the specification. Although Applicants postulate that many variants could be produced that have binding activity by making conservative substitutions outsider the CDR or FR, Applicants are arguing limitations not found in the claims and even substitutions that are expected to be conservative do not predictably function as expected for the reasons previously set forth. Although one of skill in the art would know that a large number of non-conservative amino acid substitutions in the CDRs in SEQ ID NOs:5 and 7 would likely reduce or eliminate antigen binding, Applicants are arguing limitations not found in the claims and one of skill in the art could not predictably make the broadly claimed antibody.

Applicants argue that in addition to knowing regions and residues of antibodies that would be more or less amenable to substitution or deletion, the level of knowledge and skill in the art regarding producing antibodies and antigen binding fragments thereof was also high. For example, methods of producing antibodies and variants without undue experimentation are disclosed in the specification (page 24, line 5, to page 28, line 24). Furthermore, methods of producing antibody fragments *(e.g.,* Fv, Fab, Fab' and F(ab')2) were known in the art and were routine at the time of the invention. Methods of identifying antibody variants and fragments that bind antigen without undue experimentation were also known in the art and are taught by the specification. In particular, routine methods for measuring antibody binding to antigen or cell lines, as well as methods for measuring cell proliferation and apoptosis are disclosed in the specification (page 45, line 24 to page 47, line 10; page 47, line 27, to page 49, line 14; page 56, lines 1-27; and page 57, line 19, to page 58, line 11). Applicants argue that in view of the

guidance in the specification and the high level of knowledge and skill in the art at the time of the invention regarding producing antibodies and antigen binding fragments, one skilled in the art could make antibodies and antigen binding fragments that specifically bind a polypeptide having an approximate molecular weight of 55 or 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis expressed by ASPC-1 (ATCC Accession No. CRL-1682) and BXPC-3 (ATCC Accession No. CRL-1687) which comprises a sequence at least 80% identical to the sequence of SEQ ID NO:5 or comprises a sequence at least 80% identical to the sequence of SEQ ID NO:7 without undue experimentation.

Applicants' arguments have been considered, but have not been found persuasive. Although the methods for preparation of antibodies and intact antigen binding fragments are well known in the art, the specification has not provided sufficient guidance and exemplification to make the broadly claimed antibodies given the unpredictability in the art of identifying the sequences that can be altered without affecting the function of the antibody. Although, one of ordinary skill could screen for the species that would function as claimed, in particular, screening assays do not enable the claimed invention because the court found in (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004) that screening assays are not sufficient to enable an invention because they are merely a wish or plan for obtaining the claimed chemical invention.

Applicants argue that if the skilled artisan wished to produce variants of SEQ ID NOs:5 or 7, producing recombinant proteins was routine in the art at the time of the invention, and the specification discloses routine assays for identifying antibodies that bind to the recited cell types, as discussed above. Analogous to *In re Wands,* 858 F.2d 731 (Fed. Cir. 1988), where the court held that screening hybridomas to determine those that produced monoclonal antibodies having a particular binding characteristic did not require undue experimentation, undue experimentation would not be required to identify antibody variants and fragments that bind to the recited cell types, given that 1) producing antibody variants and fragments was routine; and 2) cell binding and proliferation assays were routine at the time of the invention. Consequently, there is no need for the skilled artisan to "predict" in advance variants or fragments that bind to the recited antigen in order to make variants and antigen binding fragments. In view of the foregoing, the skilled artisan could produce antibody variants and antigen binding fragments without knowing *a priori* the effect of particular substitutions or deletions on activity.

Applicants' arguments have been considered, but have not been found persuasive. Although one could screen for hyrbridomas that have the binding activity claimed, these antibodies would not predictably have the sequence identity to SEQ ID NO: 5 or 7 claimed as the polypeptide(s) claimed are large proteins with multiple epitopes. Thus the majority of antibodies that bound to the claimed proteins would bind to distinct epitopes and would have distinct antigen binding regions, and thus would not predictably have a sequence identity to SEQ ID NO: 5 or 7. Thus, although one could screen for hyrbridomas that have the binding activity claimed they would not predictably be the broadly claimed variant antibodies comprising SEQ ID NO: 5 or 7 claimed. Although Applicant argues that one of ordinary skill could screen for the species that would function as claimed, in particular, screening assays do not enable the claimed invention because the court found in (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004) that screening assays are not sufficient to enable an invention because they are merely a wish or plan for obtaining the claimed chemical invention.

Applicants argue that the number of antibody variants and antigen binding fragments encompassed by the claims are limited as they are required to bind to antigen and therefore do not include inoperative embodiments. The claimed antibodies and fragments are further limited in number because of the high degree of sequence identity, namely at least 80% identical to the sequence of SEQ ID NO:5 or SEQ ID NO:7. Thus, the number of antibody variants and fragments encompassed by the claims will necessarily be limited based upon the functional and structural requirements of antibodies, that the antibodies and fragments will have at least partial antigen binding activity, and that the antibodies and fragments will have a sequence at least 80% identical to the sequence of SEQ ID NO:5 or SEQ ID NO:7.

Applicants' arguments have been considered, but have not been found persuasive because although the antibodies are required to bind to an antigen, one of skill in the art could not predict which of the broadly claimed antibodies will function to bind the claimed antigen for the reasons previously set forth and above.

Applicants argue that the proper standard for enablement under 35 U.S.C. §112, is whether one skilled in the art could make and use the invention without undue experimentation. In this regard, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands 858 F.2d 731,737 (Fed. Cir. 1988)

Applicants argue that here, in view of the guidance in the specification and knowledge and skill in the art concerning antibody structure and function at the time of the invention, and that antibody variants having the requisite activity could be produced and identified using routine methods disclosed in the specification or that were known in the art at the time of the invention, one skilled in the art could make antibodies and antigen binding fragments that specifically bind to the recited polypeptide without undue experimentation.

Applicants argue that first, the Examiner has acknowledged that the level of knowledge and skill with respect to antibody structure and function at the time of the invention was high. For example, as discussed at length in the Office Action the role of antibody heavy and light

chain variable regions, particularly CDRs and FRs, in antigen binding were well understood by the skilled artisan at the time of the invention. The specification also discloses the role of antibody heavy and light chain variable regions, CDR and FR regions in antigen binding (page 22, line 6, to page 23, line 2). Consequently, in view of the high level of knowledge and skill in the art with respect to antibody structure and function at the time of the invention clearly the skilled artisan would be apprised of antibody regions that participate in antigen binding.

Applicants argue that second, in addition to the high level of knowledge and skill in the art concerning antibody structure and function, as acknowledged by the Examiner the specification discloses the locations of the CDRs in SEQ ID NOs:5 and 7 (page 7 of the Office Action). In particular, the specification discloses the CDRs in SEQ ID NOs:5 and 7 in Figures 14 and 15 (see, also, pages 5, lines 6-7 and 24-25). Furthermore, in view of the fact that the specification discloses the location of the CDRs in SEQ ID NOs:5 and 7 and that SEQ ID NOs:5 and 7 are human sequences, the skilled artisan would know the location of the FRs in SEQ ID NOs:5 and 7. Consequently, the skilled artisan would know the location of CDRs and FRs of SEQ ID NOs:5 and 7.

Applicants argue that third, because the knowledge and skill in the art at the time of the invention was high in terms of antibody structure and function and the location of sequences in SEQ ID NOs:5 and 7 that contribute to antigen binding would be known, the skilled artisan would also know residues in SEQ ID NOs:5 and 7 amenable to substitution and therefore, be able to predict with reasonable certainty variants of SEQ ID NOs: 5 and 7 that would have at least partial binding activity. For example, the skilled artisan would know that an amino acid substitution, such as a conservative substitution, for example, outside of or within a CDR or FR

region of in SEQ ID NOs: 5 and 7 would likely not destroy antigen binding activity. In addition, the skilled artisan knows that antibody FRs and CDRs can tolerate substitutions.

Applicants arguments have been considered, but have not been found persuasive because claims 124 and 148 are drawn to, in part, antigen binding fragments being V_L, V_H, and F_C, and it is well established that the antigen binding domain of an antibody requires the association of the heavy and light variable chain, and the V_L, V_H, and F_C fragments would not predictably form the antigen binding domain and therefore would not predictably bind the claimed epitopes. Additionally, claims 121 and 145 encompass antibodies that retain only one 1 CDR region from SEQ ID NO:5 or 7 and neither the specification nor the art of record has shown which of these CDRs alone in combination with distinct CDRs could be used to retain binding to the claimed epitope.

Applicants argue that to corroborate that substitution within CDRs are tolerated, submitted herewith as Exhibit A is a publication by Kipriyanov et al. (Protein Engineering 10:445 (1997)). In Exhibit A the authors report that a substitution of a cysteine residue by a serine within CDR3 of an antibody heavy chain variable region did not have an adverse effect on affinity. Thus, Exhibit A corroborates that CDRs tolerate amino acid substitutions.

Applicants argue that to corroborate that substitutions within FRs are tolerated, submitted herewith as Exhibit B is a publication by Holmes et al. (J. Immunol. 167:296 (2001)). The authors of Exhibit B report several heavy chain variable region FR substitutions of an anti-lysozyme antibody did not destroy binding activity. Thus, Exhibit B corroborates that FRs tolerate substitutions.

Applicants argue that to corroborate that insertions and deletions of amino acid residues in heavy and light chain variable regions, including CDRs, are tolerated submitted herewith as Exhibit C is a publication by Wilson et al. (J. Exp. Med. 187:59 (1998)). The authors of Exhibit C report a number of insertions and deletions of variable heavy chains that occur naturally during affinity maturation which are tolerated. Thus, Exhibit C corroborates that heavy and light chain variable regions tolerate insertions and deletions.

Applicants argue that to further corroborate that insertions and deletions of amino acid residues in heavy and light chain variable regions, including CDRs, are tolerated submitted herewith as Exhibit D is a publication by Lantto and Ohlin (J. Biol. Chem. 277:45108 (2002)). The authors of Exhibit D report that single amino acid insertions or deletions of CDRs 1 and 2 of heavy chain variable region of an antibody were well tolerated. Thus, Exhibit D corroborates that heavy or light chain variable region sequences tolerate insertions and deletions, even within a CDRs.

Applicants argue that consequently, in view of the guidance in the specification and the high level of knowledge and skill in the art regarding antibody structure and function, the skilled artisan would know of general regions and particular residues that would be more or less amenable to substitution and could therefore predict SEQ ID NOs:5 and 7 variants likely to have at least partial antigen binding activity without actually having to produce such variants and fragments. Given the large number of amino residues in variable regions, clearly many variants of SEQ ID NOs:5 and 7 could be readily produced without undue experimentation that have at least partial antigen binding activity.

Applicants arguments have been considered, but have not been found persuasive because claims 124 and 148 are drawn, in part, to antigen binding fragments being V_L, V_H, and F_C, and it is well established that the antigen binding domain of an antibody requires the association of the heavy and light variable chain, and the V_L, V_H, and F_C fragments would not predictably form the antigen binding domain and therefore would not predictably bind the claimed epitopes and neither the cited references nor the specification has shown that these fragments can be used for binding to the claimed epitope. Additionally, claims 121 and 145 encompass antibodies that retain only one 1 CDR region from SEQ ID NO: 5 or 7 and neither the specification nor the art of record has shown which of these CDRs alone in combination with distinct CDRs could be used to retain binding to the claimed epitope and it is well known in the art, as previously set forth, that more than 1 CDR contributes to antibody specificity.

Applicants argue that, the level of knowledge and skill in the art regarding making antibodies and antigen binding fragments thereof was also high. For example, methods of producing antibodies and variants without undue experimentation are disclosed in the specification (page 24, line 5, to page 28, line 24). Methods of producing antibody fragments (e.g., Fv, Fab, Fab' and F(ab')2) were known in the art and were routine at the time of the invention. Methods of identifying antibody variants and fragments that bind antigen without undue experimentation were also known in the art and are taught by the specification. In particular, routine methods for measuring antibody binding to antigen or cell lines, as well as methods for measuring cell proliferation and apoptosis are disclosed in the specification (page 45, line 24 to page 47, line 10; page 47, line 27, to page 49, line 14; page 56, lines 1-27; and page 57, line 19, to page 58, line 11). Thus, in view of the guidance in the specification and the high

level of knowledge and skill in the art at the time of the invention, one skilled in the art could readily make antibodies and antigen binding fragments that specifically bind to a polypeptide having the recited molecular weight and expressed by ASPC-1 (ATCC Accession No. CRL-1682) or BXPC-3 (ATCC Accession No. CRL-1687) cells without undue experimentation.

Applicants arguments have been considered, but have not been found persuasive because methods of producing V_L, V_H, and F_C fragments that actually bind to antigen are not well known in the art and the specification has provided insufficient guidance with regard to this issue, thus one of skill in the art could not predictably make and use the invention as claimed. Additionally, methods of making an antibody that retains only 1 CDR from the parent antibody that predictably retains recognition of the parental antibody are not well known in the art and thus undue experimentation would be required to make and use the broadly claimed antibodies of claims 121 and 145 without undue experimentation for the reasons previously set forth.

Applicants argue that analogous to In re Wands, 858 F.2d 731 (Fed. Cir. 1988), where the court held that screening hybridomas to determine those that produced monoclonal antibodies having a particular binding characteristic did not require undue experimentation, undue experimentation would not be required to produce antibody variants and fragments that bind to the recited cell types, given that 1) producing antibody variants and fragments was routine; and 2) cell binding, antibody competition and proliferation assays were routine in the art at the time of the invention. Consequently, contrary to the assertion in the Office Action where it is suggested that one skilled in the art would have to "predict in advance" the sequence of antibodies within the claims, there is no need for the skilled artisan to "predict" variants or fragments that bind to the recited antigen in order to make variants and antigen binding

fragments because making antibodies and antigen binding fragments was routine and well established at the time of the invention.

Applicants arguments have been considered, but have not been found persuasive because it is well established that the antigen binding domain of an antibody requires the association of the heavy and light variable chain, and given that the V_L, V_H, and F_C fragments do not comprise the antigen binding domain, and no amount of screening would predictably result in V_L, V_H, and F_C fragments that would bind to the claimed epitope. Furthermore, given the well known contributions of the 3 CDRs to antigen binding, one of skill in the art would not be able to even predictably screen for the antibodies encompassed by claims 121 and 145 that retain only 1 CDR of SEQ ID NO: 5 or 7.

Applicants argue that finally, Applicants wish to address the citation to Rochester v. Searle 358 F.3d 916 Fed. Cir. 2004, at page 8 of the Action. The facts of Rochester are clearly distinguishable from the claims of the subject application for many reasons. In particular, in Rochester the patent at issue claimed methods of using Cox-2 inhibitors for pain and inflammation control. However, in the Rochester patent at issue there was not a single example of a Cox-2 inhibitor disclosed. Furthermore, in the Rochester patent at issue there was no guidance concerning the structure of a Cox-2 inhibitor. In stark contrast to the facts in Rochester, the specification discloses a structure, that of an antibody, which structure was well known to the skilled artisan at the time of the invention. Furthermore, the specification discloses a working example of an antibody. Moreover, the specification discloses the location of amino acid sequences of antibody light and heavy chain variable regions that contribute to antigen binding

and maintaining antibody structure. Consequently, the facts of the subject application are clearly distinguishable from Rochester.

Applicants have been considered, but have not been found persuasive. Although the structure of antibodies is well known in the art, no amount of structural information would predictably enable the binding of V_L, V_H, and F_C fragments to the claimed epitopes, for the reasons previously set forth and above, as they would not form the antigen binding domain. Additionally, the structure of the antibody normally requires the contribution of the 3 CDRs of the variable light and heavy chain and the structural information provided and known in the art does not enable one of ordinary skill in the art to make antibodies that retain only one of the CDRs of SEQ ID NO: 5 or 7 and predictably retain binding to the claimed epitope.

5. Claims 117-119 and 121 remain rejected and 141-143 and 145 are rejected under 35 U.S.C. 112, first paragraph as lacking and adequate written description for the reasons previously set forth in section 6, pages 10-16 of the Office Action of March 31, 2008.

Examiner argued:

Applicants argue that a proper analysis for written description under 35 U.S.C. § 112, first paragraph is whether one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563 (Fed. Cir. 1991); see, also, Ralston Purina Co. v. Far-Mar-Co, Inc., 772 F.2d 1570, 1575 (Fed. Cir. 1985). To satisfy the written description requirement, "Applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art." In re Angstadt, 537 F.2d 498, 502-503 (CCPA 1976), Utter v. Hiraga, 845 F.2d 993,998-99 (Fed. Cir. 1988). Thus, a description of every antibody or antigen binding fragment is not required. Furthermore, the Federal Circuit recently held "that (1) examples are not necessary to support adequacy of a written description (2) the written description standard may be met (as it is here) even where actual reduction to practice of an invention is absent; and (3) there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." Falkner v. Inglis, 448 F.3d 1357 (Fed. Cir. 2006). Thus, in view of the standard set by the court, a genus can be adequately described under 35 U.S.C. § 112, first paragraph without specific examples, an actual reduction to practice, or a complete structure of antibodies and functional fragments.

Applicants argue that in view of the guidance in the specification, which discloses antibody variable heavy and light chain sequences (e.g., SEQ ID NOs:5 and 7), and the high level of knowledge and skill in the art regarding structure and function of antibodies and antigen binding fragments the skilled artisan would be apprised of an adequate number of antibodies and antigen binding fragments within the genus of claims 111 to 133. Consequently, claims 111 to 133 are adequately described.

Applicants' arguments have been considered, but have not been found persuasive because although Applicants discloses antibody variable heavy and light chain sequences (e.g., SEQ ID NOs:5 and 7) which are the variable regions of the light and heavy chains of the monoclonal antibody PM-2, this single description of antibody that functions as claimed does not describe the broadly claimed genus of antibodies or antigen binding fragments thereof that specifically binds a polypeptide having an approximate molecular weight of 55 or 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, and wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) and BXPC-3 (ATCC Accession No. CRL-1687) which varies significantly in structure from the exemplified antibody.

Applicants argue that as discussed above, the specification teaches antibody heavy and light chain variable sequences (e.g., SEQ ID NOs:5 and 7). The specification also teaches the position of the three CDRs in each heavy and light chain variable region sequence, and therefore the position of the flanking regions (FR). In view of the foregoing guidance in the specification, one skilled in the art would know the location of the amino acid sequences that contribute to antigen binding.

Applicants' arguments have been considered, but have not been found persuasive. Although the positions of the CDRs and FRs are known, the single example of PM-2 does not provide written of the broadly claimed genus of variants whose alterations are unknown.

Applicants argue that as also discussed above, the level of knowledge and skill in the art with respect to antibody structure and function was high at the time of the invention. Evidence of such knowledge regarding antibody structure and function, such as native antibodies having two heavy and light chain sequence, the presence and contribution of three CDRs to binding, and the role of FRs is acknowledged in the Office Action and is taught by the specification. Thus, in view of the high degree of knowledge and skill in the art concerning antibody structure and function at the time of the invention, when combined with the guidance of the specification of the heavy and light chain variable sequences, SEQ ID NOs:5 and 7, the location of the CDRs and FRs that contribute to antigen binding, the molecular weights of the antigen and the cells types expressing the antigen, and the high degree of sequence identity to SEQ ID NOs:5 or 7, the skilled artisan would know variants of SEQ ID NOs:5 and 7 that would retain at least partial antigen binding activity. As an illustration, the skilled artisan would know that a conservative substitution outside of a CDR or FR of either SEQ ID NOs:5 or 7 would retain at least partial antigen binding activity. Given the number of amino residues outside of the CDR and FR regions, and the large number of amino residues outside of antibody variable regions, clearly the skilled artisan could readily envision a number of antibody variants and antigen binding fragments within the scope of the claims that have at least partial antigen binding activity of SEQ ID NOs:5 and 7. Consequently, the skilled artisan would be apprised of a number of antibodies and antigen binding fragments within the scope of the claims.

Applicants' arguments have been considered, but have not been found persuasive because, contrary to Applicants' arguments, one of skill in the art would not predictably know where to make the broadly claimed changes given the unpredictability in the art previously set forth and the lack of guidance provided in the specification. Although Applicants postulate that many variants could be produced that have binding activity by making conservative substitutions outsider the CDR or FR, Applicants are arguing limitations not found in the claims and even substitutions that are expected to be conservative do not predictably function as expected as previously set forth. Given that specification only discloses the PM-2 that binds as claimed Applicants does not provide an adequate description of the broadly claimed genus of antibodies antigen binding fragments thereof that specifically binds a polypeptide having an approximate molecular weight of 55 or 115 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, and wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) and BXPC-3 (ATCC Accession No. CRL-1687).

Applicants argue that in terms of a description of the claimed antibodies and antigen binding fragments to distinguish them from other materials, as discussed above the antibodies and antigen binding fragments are described 1) structurally- they have a high percentage of identity (at least 80%) to heavy or light chain variable sequences, SEQ ID NOs:5 and 7; and 2) functionally- they bind to a polypeptide having an approximate molecular weight of 55 or 110 kDa using SDS- PAGE, wherein the polypeptide is expressed by ASPC-1 and BXPC-3 cells. Thus, as the claimed antibodies and antigen binding fragments are described structurally- they have a heavy or light chain sequence with high degree of sequence identity to SEQ ID NOs:5 and 7, and functionally- they bind to an antigen specified by molecular weight and expressed on particular cells, the antibodies and antigen binding fragments are adequately distinguished from other materials.

Applicants' arguments have been considered, but have not been found persuasive because Applicants have only described a single species that functions as claimed thus Applicants have not provided an adequate description of the broadly claimed species for the reasons set forth above and previously.

Applicants argue that in terms of the concern regarding a description of the antigen to which the antibodies bind, as discussed above the antigen is defined in terms of molecular weight. As also discussed above, the antigen to which the claimed antibodies bind is expressed by the specified cell types. Finally, the antigen is defined based upon its binding to antibody an antibody comprising SEQ ID NOs: 5 and 7. Thus, the antigen can be considered described in view of the specified molecular weight, expression on the two specified cell types and the antibody to which the antigen binds. Furthermore, as discussed above the written description requirement may be satisfied without examples or an actual reduction to practice. In view of the fact that 35 U.S.C. §112, first paragraph does not require examples or an actual reduction to practice, clearly the written description requirement can be satisfied without actually isolating or sequencing the antigen to which the claimed antibodies and fragments bind.

Applicants' arguments have been considered, but have not been found persuasive because the description by approximate molecular weight and the cell in which the antigen is expressed is insufficient to describe the antigen. Given the variability in molecular weight determinations this description does not provide enough structural information to show possession of the claimed

antigen and one of skill in the art cannot readily recognize the identity of members of the genus. Thus Applicants have not provided an adequate description of the broadly claimed genus.

Applicants argue that moreover, because the written description requirement under 35 U.S.C. § 112, first paragraph may be satisfied without examples or an actual reduction to practice, the written description requirement can be satisfied if the skilled artisan knows of a number of antibody and antigen binding fragment of species within the claimed genus. Here, in view of the high level of knowledge and skill in the art with respect to antibody structure and function and the guidance in the specification as to the locations of CDRs and FRs in SEQ ID NOs:5 and 7 that participate in antigen binding, clearly the skilled artisan would readily envision a number of antibody and antigen binding fragment species within the claimed genus. Again, as discussed above, there are many amino residues outside of the CDR and/or FR regions, such that the skilled artisan could readily envision a number of antibody variants and antigen binding fragments within the scope of the claims that have at least partial antigen binding activity.

Applicants' arguments have been considered, but have not been found persuasive because Applicants have only described a single species, the PM-2 monoclonal antibody, that functions as claimed, thus Applicants have not provided an adequate description of the broadly claimed species for the reasons set forth above and previously.

Applicants argue that the written description requirement under 35 U.S.C. §112, first paragraph is "to clearly convey the information that an applicant has invented the subject matter which is claimed." 117 re Barker, F.2d 588, 592 (CCPA 1977). A proper analysis for written description under 35 U.S.C. §112, first paragraph is whether one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563 (Fed. Cir. 1991); see, also, Ralston Purina Co. v. Far-Mar-Co, Inc., 772 F.2d 1570, 1575 (Fed. Cir. 1985). Possession is assessed from the viewpoint of one of ordinary skill in the art: "Satisfaction of this requirement is measured by the understanding of the ordinarily skilled artisan." Lockwood v. Am. Airlifles, Inc., 107 F.3d 1565, 1572 (Fed. Cir. 1997). The description needed to satisfy the requirements of 35 U.S.C. §112 "varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence ..... Since the law is applied to each invention in view of the state of the

relevant knowledge, its application will vary with differences in the state of the knowledge in the field and differences in the predictability of the science .... the law must take cognizance of the scientific facts." Capon v. Eshhar, 418 F.3d, 1349, 1357 (Fed. Cir. 2005). Thus, an adequate written description is a factual inquiry measured by one of ordinary skill in the art, that varies with the nature and scope of the invention, taking into consideration the scientific and technologic knowledge in existence in the relevant field.

Applicants argue that furthermore, to satisfy the written description requirement, "Applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art." In re Angstadt, 537 F.2d 498,502-503 (CCPA 1976), Utter v. Hiraga, 845 F.2d 993,998-99 (Fed. Cir. 1988). In this regard, "(1) examples are not necessary to support adequacy of a written description (2) the written description standard may be met (as it is here) even where actual reduction to practice of an invention is absent; and (3) there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." Falkner v. Inglis, 448 F.3d 1357 (Fed. Ch'. 2006). Thus, in view of the standard set by the court, an actual reduction to practice or disclosure of specific examples of antibodies or functional fragments within the scope of the claims is clearly not required to satisfy 35 U.S.C. §112, first paragraph.

Applicants argue that particularly relevant to the issue of a single species of polypeptide providing an adequate written description for a genus of polypeptides, is Invitrogen Corp. v. Clontech Laboratories, Inc., 429 F.3d 1052 (Fed. Cir. 2005). In Invitrogen the court held that a single embodiment of a protein (a reverse transcriptase (RT)) provided an adequate written description of claims directed to a genus of such proteins. The court reasoned that the single

disclosed protein embodiment was adequate to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph because the protein had 1) sufficient correlation between structure and function; and 2) shared significant homology with others. In affirming that the patents in-issue satisfied the written description requirement, as articulated by the court in Regents' of the University of California v. Eli Lilly & Co., 119 F.3d 1559 (1997) and Fiers v. Revel, 984 F.2d 1164 (Fed. Cir. 1993), the court held that "the shared written description for the patents-in-issue recites both the DNA and amino acid sequences of a representative embodiment of the claimed RT enzyme. The specification also discloses test data that the enzyme produced by the listed sequence has the claimed features--DNA polymerase activity without RNase H activity. Under both the Eli Lilly and Fiers analysis, the specification at bar is sufficient. In short, there is no error in the district court's ruling that the claims in the patents-in-suit satisfy the written description requirement of §112." Thus, even though there was only a single disclosed embodiment the claims of the patents in-issue in Invitrogen, which were not limited by reciting a particular amount of homology or identity to a reference sequence in the claims, were held to satisfy the written description requirement. Accordingly, in view of Invitrogen a single embodiment provides a written description for a genus of proteins where there is sufficient correlation between protein structure and function, and the members of the species share significant homology.

Applicant's arguments have been considered, but have not been found persuasive. The claims encompass antibodies that do not include 1 or more of the CDR regions of SEQ ID NO: 5 or 7 or substantial portions of the framework region of SEQ ID NO: 5 or 7. For example, an antibody that comprises a sequence that is 90% identical to 90 contiguous amino of SEQ ID

NO: 5 includes antibodies that need do not have any identity to 26 of the 116 amino acids of SEQ ID NO: 5 and the 90 contiguous amino acids can have changes in 9 additional amino acids and the CDR regions of SEQ ID NO: 5 are only 7 or 8 amino acids in length or, an antibody that comprises a sequence that is 95% identical to 90 contiguous amino of SEQ ID NO: 5 includes antibodies that need do not have any identity to 26 of the 116 amino acids of SEQ ID NO: 5 and can have changes in 6 additional amino acids in the 90 contiguous amino acids. Thus, these embodiments include antibodies of less than 75% identity to SEQ ID NO: 5 that do not contain all or a significant portion of the CDRs of SEQ ID NO: 5. A similar reasoning can be applied to SEQ ID NO: 7. Given the importance of the CDRs to antibody binding and the contributions of the framework region to binding to the epitope previously set forth, the description of the PM-2 antibody comprising SEQ ID NO: 5 and SEQ ID NO: 7 that binds to the claimed epitope does not describe an antibody lacking these CDRs, but is only a description of what it does, i.e. bind to the claimed epitope. Additionally, claims 121 and 145 that encompass antibodies that have only 1 CDR of SEQ ID NO: 5 or 7 and retain binding to the claimed epitope are not adequately described by the description of the PM-2 antibody or SEQ ID NO: 5 or 7 given the art known contributions of all CDRs to epitope recognition and the absence of a description of such an antibody that retains this activity other than PM-2 and there is not a know or disclosed correlation between structure and function of such antibodies.

Applicants argue that here, the skilled artisan has substantial understanding of antibody structure and function, and the claimed antibodies and functional fragments defined by percent identity to a heavy or light chain variable region share significant sequence homology (at least 90%) with heavy or light chain variable region sequences SEQ ID NOs:5 and 7. Furthermore, the

specification discloses a working example having binding activity within the genus. Consequently, given the correlation between antibody structure and function, that the antibodies defined by percent identity share significant sequence homology to SEQ ID NOs:5 or 7, and that the specification discloses an embodiment within the genus having binding activity, clearly the claims meet the written description standard as articulated by the court in Invitrogen. Consequently, claims 111 to 130 and 133 are adequately described.

Applicants argument have been considered, but have not been found persuasive because although a structure function correlation exists for the intact antibody comprising SEQ ID NO: 5 and 7 with the full complement of CDRs and intact framework region, no structure function correlation has been established for antibodies that lack 1 or more CDRs of SEQ ID NO: 5 or 7 or a substantial portion of the framework region of SEQ ID NO: 5 or 7 that still bind the claimed epitopes.

Applicants argue that as discussed above, the specification teaches antibody heavy and light chain variable sequences (e.g., SEQ ID NOs:5 and 7). The specification also teaches the position of the three CDRs in each heavy and light chain variable region sequence, and therefore the position of the flanking regions (FR). In view of the foregoing guidance, one skilled in the art would know the location of the amino acid sequences that contribute to antigen binding.

Applicants argue that as also discussed above, the level of knowledge and skill in the art with respect to antibody structure and function was high at the time of the invention. Evidence of such knowledge, such as native antibodies having two heavy and light chain sequence, the presence and contribution of three CDRs to binding, and the role of FRs is acknowledged in the Office Action and is taught by the specification. Thus, in view of the high degree of knowledge

and skill in the art concerning antibody structure and function at the time of the invention, when combined with the guidance of the specification of the heavy and light chain variable sequences, SEQ ID NOs:5 and 7, the location of the CDRs and FRs that contribute to antigen binding, the molecular weights of the antigen and the cells types expressing the antigen, and the high degree of sequence identity to SEQ ID NOs:5 or 7, the skilled artisan would know variants of SEQ ID NOs:5 and 7 that would retain at least partial antigen binding activity, as discussed above and in the record. Consequently, the skilled artisan would be apprised of a number of antibodies and antigen binding fragments within the scope of the claims.

Applicant's arguments have been considered, but have not been found persuasive because the variants include antibodies that lack 1 or more CDRs of SEQ ID NO: 5 or 7 or a substantial portion of the framework region of SEQ ID NO: 5 or 7 that still bind the claimed epitopes and one of skill in the are could not readily visualize such variants based on the teachings of the specification and art of record.

Applicants argue that in terms of a description of the claimed antibodies and antigen binding fragments to distinguish them from other materials, the antibodies and antigen binding fragments are described 1) structurally- they have heavy and light chain variable region sequences, and may have at least 90% identity to SEQ ID NOs:5 or 7; and 2) functionally- they bind to a polypeptide having an approximate molecular weight of 55 or 110 kDa using SDS-PAGE, and the polypeptide is expressed by ASPC-1 or BXPC-3 cells. Thus, as the claimed antibodies and antigen binding fragments are described structurally and functionally, the antibodies and antigen binding fragments are adequately distinguished from other materials.

In terms of the concern regarding a description of the antigen to which the antibodies bind, as discussed above the polypeptide is defined in terms of molecular weight. As also discussed above, the polypeptide is expressed by the specified cell types. Finally, the polypeptide is defined based upon its binding to antibody comprising SEQ ID NOs:5 and 7. Thus, the antigen is described in terms of the specified molecular weight, cell type expression and the antibody that the antigen binds.

Applicants argue that furthermore, as discussed above the written description requirement may be satisfied without examples or an actual reduction to practice. Consequently, clearly the written description requirement of 35 U.S.C. § 112, first paragraph can be satisfied without actually isolating or sequencing the antigen to which the claimed antibodies and fragments bind.

Applicants argue that in sum, in view of the guidance in the specification and the substantial understanding of antibody structure and function at the time of the invention, and the degree of sequence identity of the claimed antibodies and functional fragments to SEQ ID NOs:5 or 7, as corroborated by Exhibits A-D, the skilled artisan would be apprised of a number of antibodies and functional fragments of claims. Furthermore, in view of the substantial understanding of antibody structure and function, the significant sequence homology required by the dependent claims, and that the specification discloses an embodiment having activity, clearly the claims meet the standard for written description articulated by the court in Invitrogen. Consequently, claims 111 to 122, 124 to 130 and 133 are adequately described under 35 U.S.C. § 112, first paragraph, and Applicants respectfully request that the rejection be withdrawn.

Applicant's arguments have been considered, but have not been found persuasive because the variants include antibodies that lack 1 or more CDRs of SEQ ID NO: 5 or 7 or a substantial

portion of the framework region of SEQ ID NO: 5 or 7 that still bind the claimed epitopes and one of skill in the are could not readily visualize such variants based on the teachings of the specification and art of record.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 111-122 and 126-130 remain rejected and claims 123, 133-147, and 150-154 are rejected under 35 U.S.C. 102(b) as being anticipated by Brändlein et al. (Amer. Assoc. Can. Res., March 29, 2002, 43:970, abstract #4803, IDS) as evidenced by Brändlein et al. (Human Antibodies, 18 April 2003, 11:107-119, IDS), for the reasons previously set forth in section 13, pages 40-44 of the Office Action of July 31, 2007.

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration In re Spada, 911 F.2d 705 (Fed. Cir. 1990), In re Bond, 910 F.2d 831 (Fed. Cir. 1990). Furthermore, a reference cited under section 102 must contain an enabling disclosure, citations omitted, see, M.P.E.P. §2121.

Applicants argue that as a first issue, Applicants respectfully point out that a reference cited under 35 U.S.C. §102 must have an enabling disclosure. Thus, for this rejection to be proper, Brandlein et al. (Amer. Assoc. Cancer Res. 43:970 abstract #4803 (2002)) must enable one skilled in the art to make and use claims 111 to 123 and 126 to 130 without undue experimentation. However, these claims have also been rejected under 35 U.S.C. §112, first

paragraph, as allegedly lacking enablement. Consequently, the rejections under 35 U.S.C. §102(b) and 35 U.S.C. §112, first paragraph are contradictory and cannot be maintained simultaneously. Applicants therefore respectfully request that the Patent Office withdraw either the rejection under 35 U.S.C. § 102(b) or the rejection under 35 U.S.C. § 112, first paragraph.

Applicants' arguments have been considered, but have not been found persuasive. As previously set forth, the enablement rejection in section 7 of the Office Action of July 31, 2007, was a scope of enablement rejection with the enabled species being the PM-2 monoclonal antibody comprising SEQ ID NO: 5 and 7. Given that Brändlein et al. is co-authored by the inventors of the instant invention and the PM-2 antibody was produced by the same method as that of the instant invention and exhibits the same properties as the antibody of the instant invention, the product of the prior art comprises the same product as claimed in the instant invention and this species is enabled.

Applicants argue that as a second issue, Brandlein et al. (Amer. Assoc. Cancer Res. 43:970 abstract #4803 (2002)) at best mention the term "PM-2"- there is no information concerning the nature of the antigen to which PM-2 binds, such as molecular weight. Nor is there any information in the abstract concerning how to produce PM-2 antibody or a source of PM-2 antibody, or a heavy or light chain variable region sequence, such that one skilled in the art could obtain or produce PM-2 antibody or a variant antibody or subsequence thereof, without undue experimentation. Absent antigen information, antibody sequence or a source or method to obtain or produce PM-2 antibody one skilled in the art could not produce the antibody without undue experimentation. Consequently, Brandlein et al. (Amer. Assoc. Cancer Res. 43:970 abstract #4803 (2002)) fail to enable claims 111 to 123 and 126 to 130. Applicants argue that in sum,

Brandlein et al. (Amer. Assoc. Cancer Res. 43:970 abstract #4803 (2002)) fail to enable claims 111 to 123 and 126 to 130.

Applicants' arguments have been considered, but have not been found persuasive because Brändlein et al. is co-authored by the inventors of the instant invention and the PM-2 antibody was produced by the same method as that of the instant invention and exhibits the same properties as the antibody of the instant invention, the product of the prior art comprises the same product as claimed in the instant invention, thus the PM-2 monoclonal antibody will inherently be the antibody of the instant invention comprising SEQ ID NO: 5 and 7, which is an enabled species for the reasons previously set forth and above.. The publication of Brandlein et al. before the filing date of the instant application indicates that the hybridoma producing the PM-2 antibody was publicly available and thus one of skill in the art would be able to make the antibody and obtain the sequence of the PM-2 antibody. A showing that the hybridoma producing the PM-2 antibody was not publicly available prior to the filing date of the instant application would support Applicants arguments that the Brandlein et al. was not enabled for the PM-2 antibody, hybridoma, and sequence information.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 124 and 125 remain and claims 148 and 149 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brändlein et al. (Amer. Assoc. Can. Res., 2002, 43:970, abstract #4803, IDS) as applied to claims 111-122 and 126-132 above, and in further view of Taylor (US Patent No. 5,001,225, December, 8 1986, previously cited), for the reasons previously set forth in section 9, pages 19-21 of the Office Action of March 31, 2008.

Applicants argue that at the time of the invention: 1) a suggestion or motivation to modify or combine the references at the time of the invention; 2) a reasonable expectation of success of producing the claimed invention; and 3) the combined references must teach or suggest each and every claim limitation. Both the teaching or suggestion to make the claimed combination and reasonable expectation of success must both be found in the prior art, not in Applicants' disclosure. See, e.g., In re Vaeck, 947 F.2d 488 (Fed. Cir. 1991) and In re O'Farrell, 853 F.2d 894, 903-904 (Fed. Cir. 1988). [R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. In re Kahn, 441 F.3d 977, 988 (Fed. Cir. 2006); see also, KSR International Co., v. Tele[lex Inc., 82 U.S.PQ. 1385, 1396 (U.S. 2007)- "a patent composed of several elements is not proved obvious by merely demonstrating that each of its elements was, independently, known in the prior art.

Applicants argue that here, among other things, there would not have been a reasonable expectation of success of producing the claimed antibodies in view of Brandlein et al (Amer. Assoc. Cancer Res, 43:970 abstract #4803 (2002)). As discussed above, the cited abstract fails to teach or suggests anything concerning the nature of the antigen to which PM-2 binds. Nor is there any information in the cited abstract concerning how to produce PM-2 antibody or a source

of PM-2 antibody. Furthermore, the abstract fails to describe any heavy or light chain variable region antibody sequences. Thus, in view of the foregoing deficiencies, one skilled in the art could not obtain or produce PM-2 antibody or a variant antibody or subsequence thereof with a reasonable expectation of success. Consequently, Brandlein et al. (Amer. Assoc. Cancer Res. 43:970 abstract #4803 (2002)) fail to teach or suggest each and every element of claims 124 and 125.

Applicants' arguments have been considered, but have not been found persuasive. The publication of Brandlein et al. before the filing date of the instant application indicates that the hybridoma producing the PM-2 antibody was publicly available and thus one of skill in the art would be able to make the antibody and obtain the sequence of the PM-2 antibody. A showing that the hybridoma producing the PM-2 antibody was not publicly available prior to the filing date of the instant application would support Applicants arguments that the Brandlein et al. was not enabled for the PM-2 antibody, hybridoma, and sequence information.

Applicants argue that the secondary reference of Taylor et al. (US Patent 5,001,225) fails to provide that which is missing from Brandlein et al. (Amer. Assoc. Cancer Res. 43:970 abstract #4803 (2002)). In this regard, there is no sequence described in Taylor et al. at least 80% identical to the sequence of SEQ ID NO:5 or SEQ ID NO:7. Consequently, Brandlein et al. (Amer. Assoc. Cancer Res. 43:970 abstract #4803 (2002)) and Taylor et al. (US Patent 5,001,225) fail to teach or suggest each and every element of claims 124 and 125.

Applicants arguments have been considered, but have not been found persuasive because Applicants are arguing limitations, a sequence at least 80% identical to the sequence of SEQ ID

NO:5 or SEQ ID NO:7, that is not found in the claims. Furthermore, the PM2 antibody would be an antibody species within said genus.

Applicants argue that Lastly, if the Patent Office maintains that one skilled in the art would have been able to obtain PM-2 antibody based upon the cited abstract and Taylor et al. (US Patent 5,001,225) at the time of the invention, Applicants respectfully again note that "[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." In re Kahn, 441 F.3d 977, 988 (Fed. Cir. 2006) Thus, the Office must explain how the antibody would have been obtained or produced, given the information in the cited abstract and Taylor et al. (US Patent 5,001,225), at the time of the invention.

Applicants argue that in sum, Brandlein et al. (Amer. Assoc. Cancer Res. 43:970 abstract #4803 (2002)) alone or in combination with Taylor et al. (US Patent 5,001,225) fail to teach or suggest each and every element of claims 124 and 125, and fail to provide a reasonable expectation of success of producing an antibody or an antigen binding fragment of claims 124 and 125.

Applicants' arguments have been considered, but have not been found persuasive. The publication of Brandlein et al. before the filing date of the instant application indicates that the hybridoma producing the PM-2 antibody was publicly available and thus one of skill in the art would be able to make the antibody and obtain the sequence of the PM-2 antibody. Thus, given that Taylor teaches that Fab and $F(ab')_2$ fragments lacking the Fc fragment of an antibody, clear more rapidly from circulation and have less nonspecific tissue binding than intact antibody (col

9, lines 22-25) and further teach that Fab, F(ab')2 fragments may be used as well as the intact antibody in methods of detection and treatment (col 9, lines 26-32) and given that Taylor also teaches labeling the antibody of the invention by well known art methods, see Col. 9, lines 33-45, one of skill in the art would be able to make and produce the PM-2 antibody and the Fab, F(ab'), and $F(ab')_2$ fragments thereof.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 135-154 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 135 recites the limitation " said epitope of the polypeptide having an approximate molecular weight of 115 kDa expressed by ASPC-1 (ATCC Accession No. CRL-1682) or BXPC-3 (ATCC Accession No. CRL- 1687) cells ". There is insufficient antecedent basis for this limitation in the claim as the claim preceding the wherein clause is drawn to " A purified antibody or antigen binding fragment thereof, wherein said antibody or said antigen binding fragment specifically binds to an epitope of a polypeptide having an approximate molecular weight of 55 kDa using sodium dodecyl sulfate polyacrylamide gel electrophoresis, wherein said polypeptide is expressed by ASPC-1 (ATCC Accession No. CRL-1682) or BXPC-3 (ATCC Accession No. CRL-1687) cells". Amendment of the claimed to " said epitope of the polypeptide having an approximate molecular weight of **55** kDa expressed by ASPC-1 (ATCC

Accession No. CRL-1682) or BXPC-3 (ATCC Accession No. CRL- 1687) cells" would obviate this rejection.

9. No claims allowed

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571)272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Helms Larry can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Peter J Reddig/
Examiner, Art Unit 1642

/Karen A Canella/
Primary Examiner, Art Unit 1643